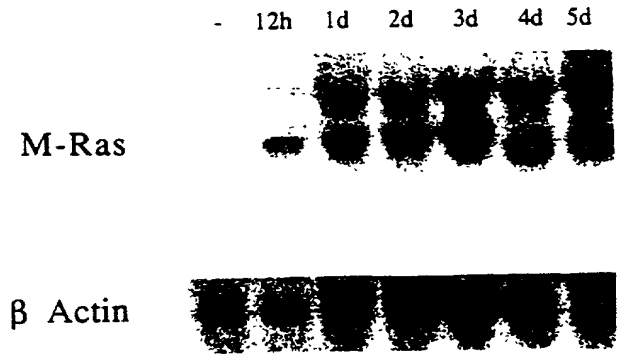
```
     GGCCTGACTACCAGAAAC ATG GCG ACC AGC GCT GTT CCA AGT GAA AAC CTT CCC ACA TAT     60
                        M   A   T   S   A   V   P   S   E   N   L   P   T   Y      14

AAA CTA GTA GTG GTG GGA GAT GGT GGT GTG GGC AAG AGT GCG CTC ACT ATT CAG TTT TTC   120
 K   L   V   V   V   G   D   G   G   V   G   K   S   A   L   T   I   Q   F   F    34

CAG AAG ATC TTT GTG CCT GAC TAC GAC CCC ACC ATT GAA GAC TCC TAC CTG AAG CAT ACA   180
 Q   K   I   F   V   P   D   Y   D   P   T   I   E   D   S   Y   L   K   H   T    54

GAG ATT GAC AAT CAG TGG GCC ATC TTG GAT GTT CTG GAC ACA GCC GGG CAG GAG GAG TTC   240
 E   I   D   N   Q   W   A   I   L   D   V   L   D   T   A   G   Q   E   E   F    74

AGT GCC ATG CGG GAA CAA TAC ATG CGC ACA GGG GAT GGC TTC CTC ATT GTC TAC TCC GTC   300
 S   A   M   R   E   Q   Y   M   R   T   G   D   G   F   L   I   V   Y   S   V    94

ACC GAC AAG GCC AGC TTC GAG CAC GTG GAC CGC TTC CAC CAG CTC ATT CTG CGT GTC AAG   360
 T   D   K   A   S   F   E   H   V   D   R   F   H   Q   L   I   L   R   V   K   114

GAC AGG GAG TCA TTC CCA ATG ATC CTC GTG GCC AAC AAG GTG GAT CTG ATG CAC CTA AGG   420
 D   R   E   S   F   P   M   I   L   V   A   N   K   V   D   L   M   H   L   R   134

AAA GTC ACC AGG GAC CAA GGA AAA GAA ATG GCA ACC AAA TAC AAT ATC CCA TAT ATA GAG   480
 K   V   T   R   D   Q   G   K   E   M   A   T   K   Y   N   I   P   Y   I   E   154

ACC AGT GCC AAG GAC CCG CCT CTC AAC GTG GAT AAA ACC TTC CAT GAC CTA GTT AGA GTA   540
 T   S   A   K   D   P   P   L   N   V   D   K   T   F   H   D   L   V   R   V   174

ATT AGG CAA CAG GTT CCA GAG AAA AAC CAG AAG AAG AAA AAG AAG ACA AAA TGG CGA GGA   600
 I   R   Q   Q   V   P   E   K   N   Q   K   K   K   K   T   K   W   R   G   194

GAC AGG GCC ACC GGC ACT CAC AAA CTG CAG TGT GTC ATC TTG TGA CAG CCT GAA GCC CTG   660
 D   R   A   T   G   T   H   K   L   Q   C   V   I   L   *                       208

GGCATAGCAACCGTGAACTGCCAGCCCCTGGGACCAGCCCACTGCCTAACTGCACTGAGAACCACTTCTAACTACAGCC   739
CTTGGCTCTTGGACTGGGCATTGGAAGGGAATGAGGGAGGAGGGGGCAGAAGCAGGCCGGGGCTGGCTTTGCTGCCTGT   818
CCCAGGAGACAGGGCTACAGCTTCCAAACCTTTTGTGTGTTGACTGAGCCCAGTTCCCAGTCTCTTGGTGGGCTTGTTT   897
CTTTTAACTCATAGGCTGGTTTGCTATGGAAGTGCTTACCCACATACAACGCACCAGACAAGCCATGAGCAAGCTTCCT   976
CCCTGTCCCATCCCCAGTGTCTGAGCTCTTGTGTCTTTTGTAGATTTTTAAATTATTTGAGTAATGATTATTTTATTAA  1055
AGAGGTCTGTGCCCATTGCCTGCGAAGCCCCAAGTCTTTGGCAGACCTCTGATAAATGTCTGCA                  1119
```

**Figure 1**

```
p21 Ras   MT-------------------------EYKLVVVGAGGVGKSALTIQLI   24
M-Ras     MATSAV--------------PSENLP--TYKLVVVGDGGVGKSALTIQFF   34
R-Ras     MSSGAASGTGRGRPRGGGPGPRDPPPGETHKLVVVGGGGVGKSALTIQFI   50

p21 Ras   QNHFVDEYDPTIEDSYRKQVVIDGETCLLDYLDTAGQEEYSAMRDQYMRT   74
M-Ras     QKIFVPDYDPTIEDSYLKHTEIDNQWAILDVLDTAGQEEFSAMREQYMRT   84
R-Ras     QSYFVSDYDPTIEDSYTKICTVDGIPARLDILDTAGQEEFGAMREQYMRA  150

p21 Ras   GEGFLCVFAINNTKSFEDIHQYREQIKRVKDSDDVPMVLVGNKCDLAA-R  123
M-Ras     GDGFLIVYSVTDKASFEHVDRFHQLILRVKDRESFPMILVANKVDLMHLR  134
R-Ras     GNGFLLVFAINDRQSFNEVGKLFTQILRVKDRDDFPIVLVGNKADLENQR  150

p21 Ras   TVESRQAQDLARSYGIPYIETSAK-TRQGVEDAFYTLVREIRQHKLRKLN  172
M-Ras     KVTRDQGKEMATKYNIPYIETSAKDPPLNVDKTFHDLVRVIRQQVPEKNQ  184
R-Ras     QVLRSEASSFSASHHMTYFEASAK-LRLNVDEAFEQLVRAVRKYQEQELP  199

p21 Ras   PPDESGP----GCMSC---KCVLS                           189
M-Ras     KKKKKTKWRGDRATGTHKLQCVIL                           208
R-Ras     PSPPSAPRK--KDGGC---PCVLL                           218
```

**Figure 2**


- 12h 1d 2d 3d 4d 5d
M-Ras
β Actin

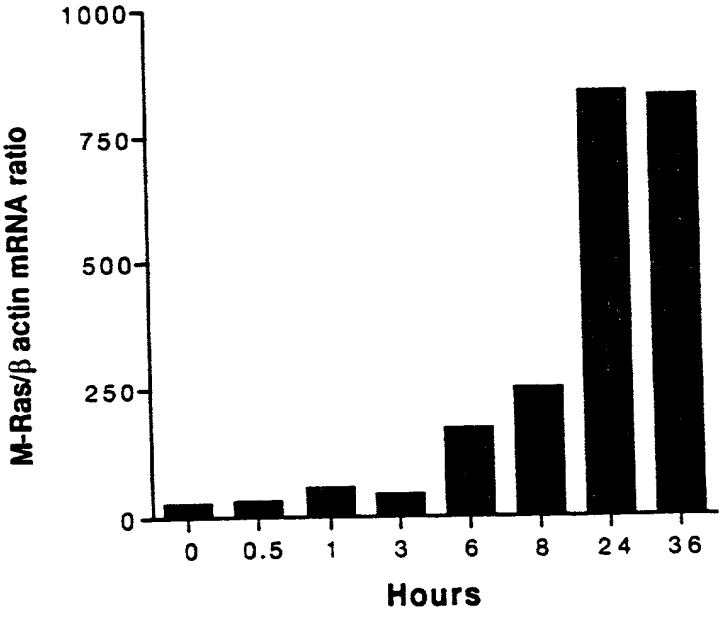

1000
750
500
250
0
M-Ras/β actin mRNA ratio
0 0.5 1 3 6 8 24 36
Hours

**Figure 3**

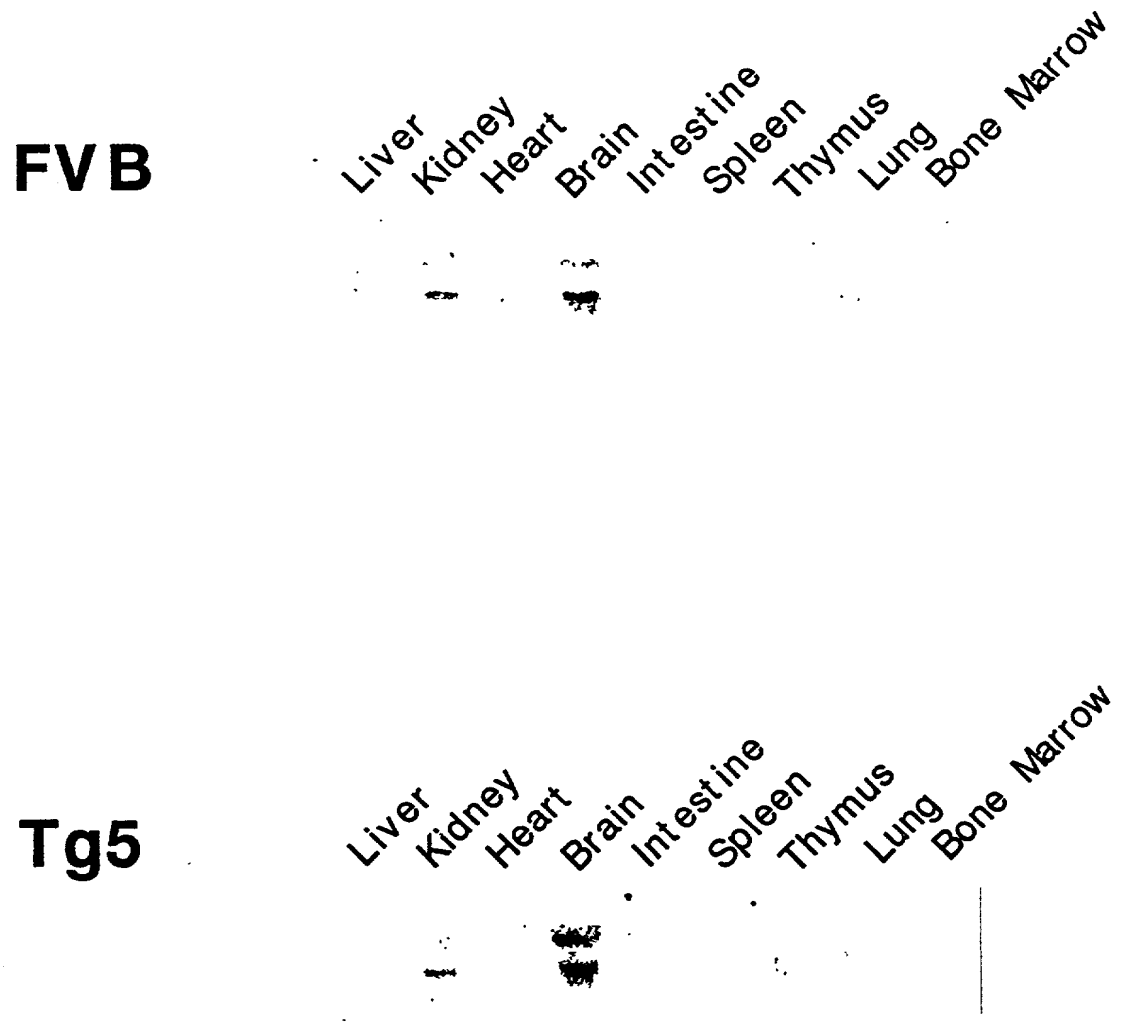

FVB
Liver
Kidney
Heart
Brain
Intestine
Spleen
Thymus
Lung
Bone Marrow
Tg5
Liver
Kidney
Heart
Brain
Intestine
Spleen
Thymus
Lung
Bone Marrow

Figure 4

```
                                                                CGGCGGCGACGCTGCCTCCTCACCGGCGCAGGCTAGGAGGGGGCGG    46

CCTGAGTGCCGTAGCCGAGCCGGGGCTGGAGCGCGCGGTCTGACCTACGAGAAAC ATG GCA ACC AGC GCC GTC   120
                                                          M   A   T   S   A   V     6

CCC AGT GAC AAC CTC CCC ACA TAC AAG CTG GTG GTG GTG GGG GAT GGG GGT GTG GGC AAA   180
 P   S   D   N   L   P   T   Y   K   L   V   V   V   G   D   G   G   V   G   K    26

AGT GCC CTC ACC ATC CAG TTT TTC CAG AAG ATC TTT GTG CCT GAC TAT GAC CCC ACC ATT   240
 S   A   L   T   I   Q   F   F   Q   K   I   F   V   P   D   Y   D   P   T   I    46

GAA GAC TCC TAC CTG AAA CAT ACG GAG ATT GAC AAT CAA TGG GCC ATC TTG GAC GTT CTG   300
 E   D   S   Y   L   K   H   T   E   I   D   N   Q   W   A   I   L   D   V   L    66

GAC ACA GCT GGG CAG GAG GAA TTC AGC GCC ATG CGG GAG CAA TAC ATG CGC ACG GGG GAT   360
 D   T   A   G   Q   E   E   F   S   A   M   R   E   Q   Y   M   R   T   G   D    86

GGC TTC CTC ATC GTC TAC TCC GTC ACT GAC AAG GCC AGC TTT GAG CAC GTG GAC CGC TTC   420
 G   F   L   I   V   Y   S   V   T   D   K   A   S   F   E   H   V   D   R   F   106

CAC CAG CTT ATC CTG CGC GTC AAA GAC AGG GAG TCA TTC CCG atG atC CTC GTG GCC AAC   480
 H   Q   L   I   L   R   V   K   D   R   E   S   F   P   M   I   L   V   A   N   126

AAG GTC GAT TTG ATG CAC TTG AGG AAG ATC ACC AGG GAG CAA GGA AAA GAA ATG GCG ACC   540
 K   V   D   L   M   H   L   R   K   I   T   R   E   Q   G   K   E   M   A   T   146

AAA CAC AAT ATT CCG TAC ATA GAA ACC AGT GCC AAG GAC CCA CCT CTC AAT GTC GAC AAA   600
 K   H   N   I   P   Y   I   E   T   S   A   K   D   P   P   L   N   V   D   K   166

GCC TTC CAT GAC CTC GTT AGA GTA ATT AGG CAA CAG ATT CCG GAA AAA AGC CAG AAG AAG   660
 A   F   H   D   L   V   R   V   I   R   Q   Q   I   P   E   K   S   Q   K   K   186

AAG AAG AAA ACC AAA TGG CGG GGA GAC CGG GCC ACA GGC ACC CAC AAA CTG CAA TGT GTG   720
 K   K   K   T   K   W   R   G   D   R   A   T   G   T   H   K   L   Q   C   V   206

ATC TTG TGA GGCCTGCAGGCCTGAAGGCCTCGGGCACAGTGACGGTGGCCTGGCCAGCCCTCGGGACCCCTCCCCA  791
 I   L   *                                                                       208

CCTAACTGCACTGAAACCATTTCTAACCACAACCCTTGGCCCAAGGACTTGGTACAGGAAGGGAGAAGGGCAGGTGGGC  870
AGGGAGCAAGACAGGGTCTGGCTTTTGCCAAGAGGAACGGGGCTTTTTCCACCTTCTTCAAAAGAGACAAGGGAAGGCC  949
ACCTGTTAAAGCAGGAAGCAGCATCAAGTTGCCCCTTGGGCCCCCCCCATGTTGTTTGGATTTCAAACCGGGTTTCCTTC 1028
CCCCTTCTTTTCGGGTTGGGTGTTGTTGGTTATTTGGTTAACTACATATGGTT                            1081
```

**Figure 5**

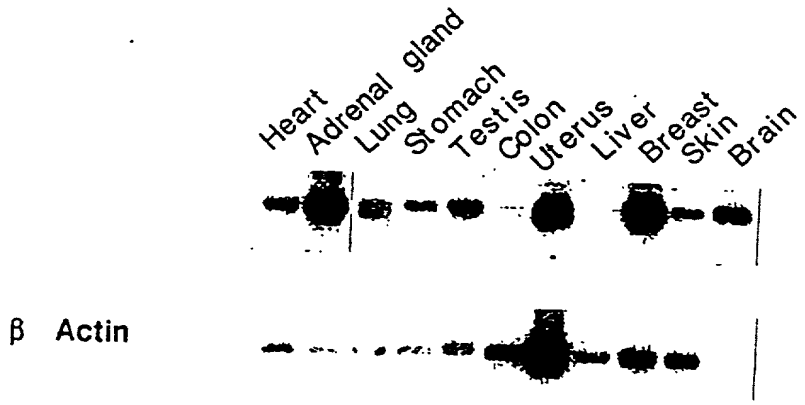

Heart
Adrenal gland
Lung
Stomach
Testis
Colon
Uterus
Liver
Breast
Skin
Brain
β Actin

**Figure 6**

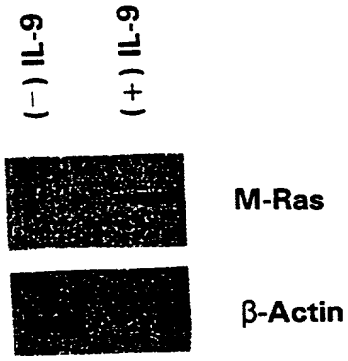



Figure 7

| | Constitutively Activated | | | Dominant Negative | |
|---|---|---|---|---|---|
| M-Ras | M-Ras-1 | M-Ras-2 | M-Ras-3 | M-Ras-4 | M-Ras-5 |
| | G22→V22 | Q71→K71 | G22→K22 | S27→N27 | C205→S205 |
| | GGT→GTT | CAG→AAA | GGT→AAG | AGT→AAT | TGT→TCT |

Figure 8

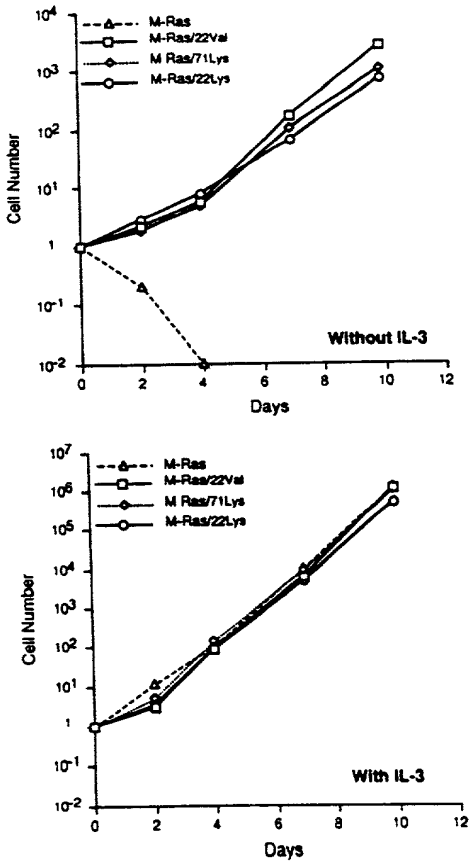

M-Ras
M-Ras/22Val
M Ras/71Lys
M-Ras/22Lys
Cell Number
Without IL-3
Days
M-Ras
M-Ras/22Val
M Ras/71Lys
M-Ras/22Lys
Cell Number
With IL-3
Days

**Figure 9**

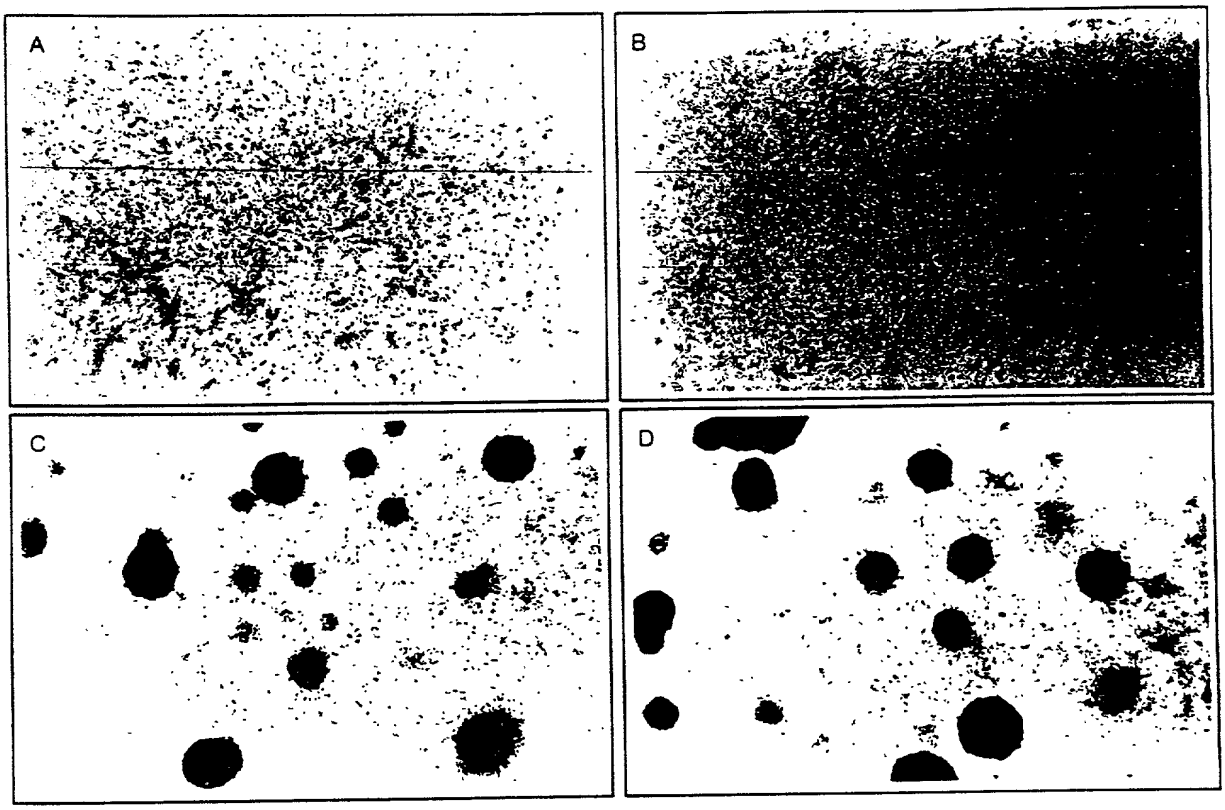



**Figure 10**

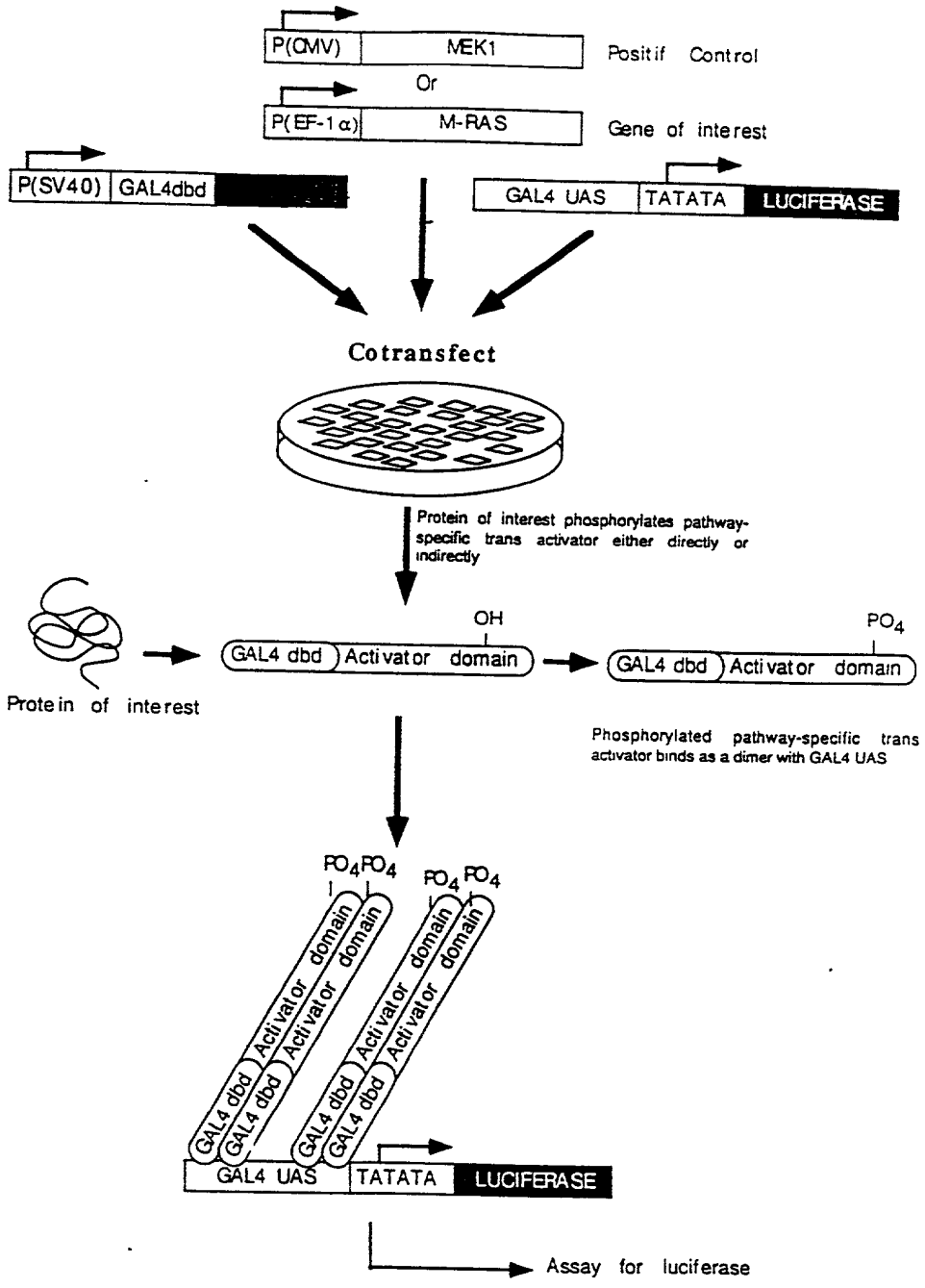

P(CMV)
MEK1
Positif Control
Or
P(EF-1α)
M-RAS
Gene of interest
P(SV40)
GAL4dbd
GAL4 UAS
TATATA
LUCIFERASE
Cotransfect
Protein of interest phosphorylates pathway-specific trans activator either directly or indirectly
OH
PO4
GAL4 dbd
Activator domain
Protein of interest
Phosphorylated pathway-specific trans activator binds as a dimer with GAL4 UAS
PO4PO4
PO4 PO4
GAL4 dbd
Activator domain
GAL4 UAS
TATATA
LUCIFERASE
Assay for luciferase

**Figure 11**

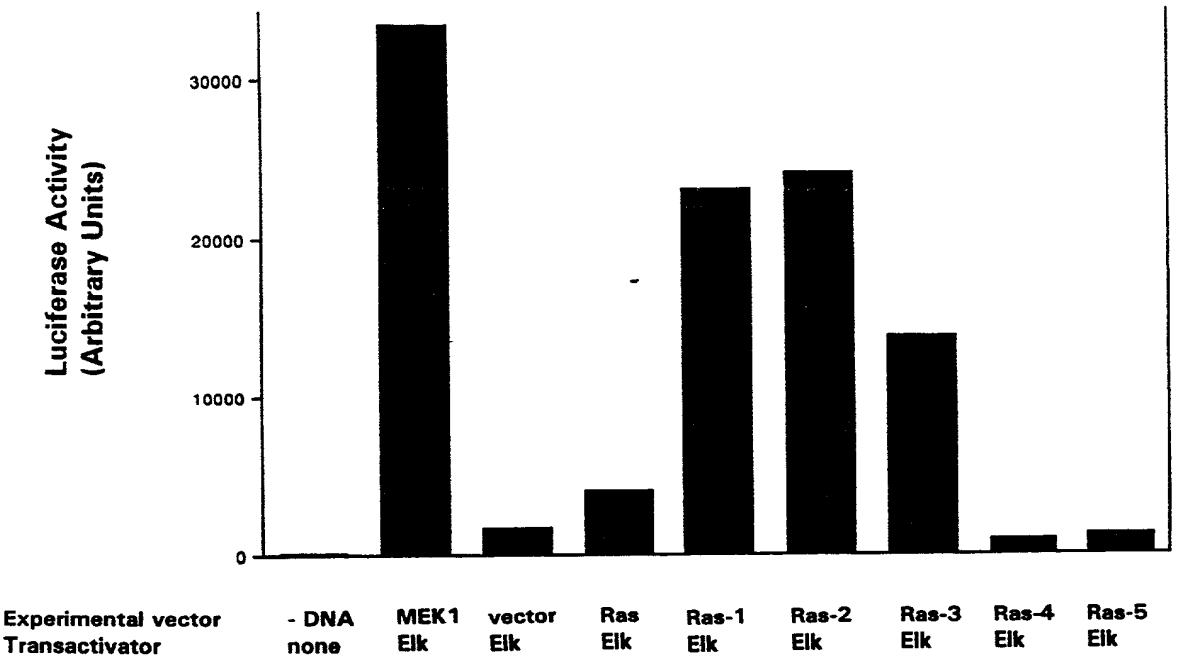

Luciferase Activity
(Arbitrary Units)
30000
20000
10000
0
Experimental vector
Transactivator
- DNA
none
MEK1
Elk
vector
Elk
Ras
Elk
Ras-1
Elk
Ras-2
Elk
Ras-3
Elk
Ras-4
Elk
Ras-5
Elk

Figure 12

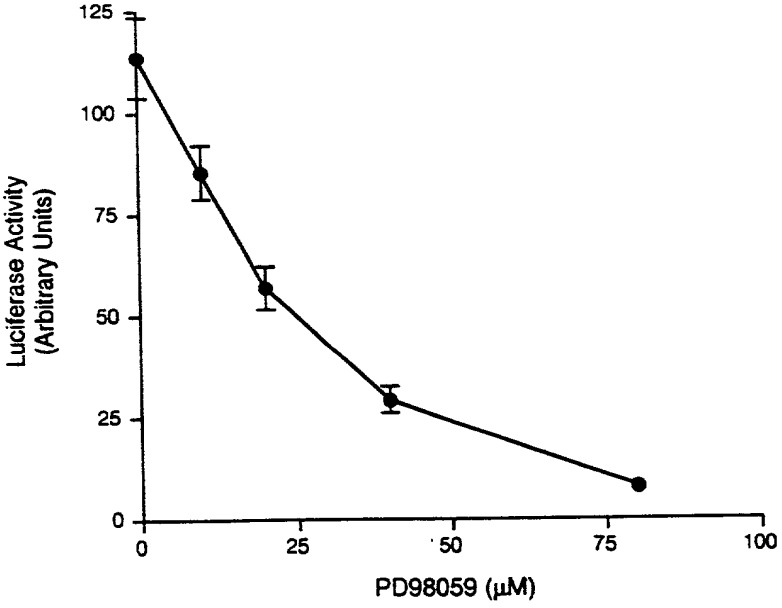

125
100
75
50
25
0
Luciferase Activity
(Arbitrary Units)
0
25
50
75
100
PD98059 (μM)

**Figure 13**

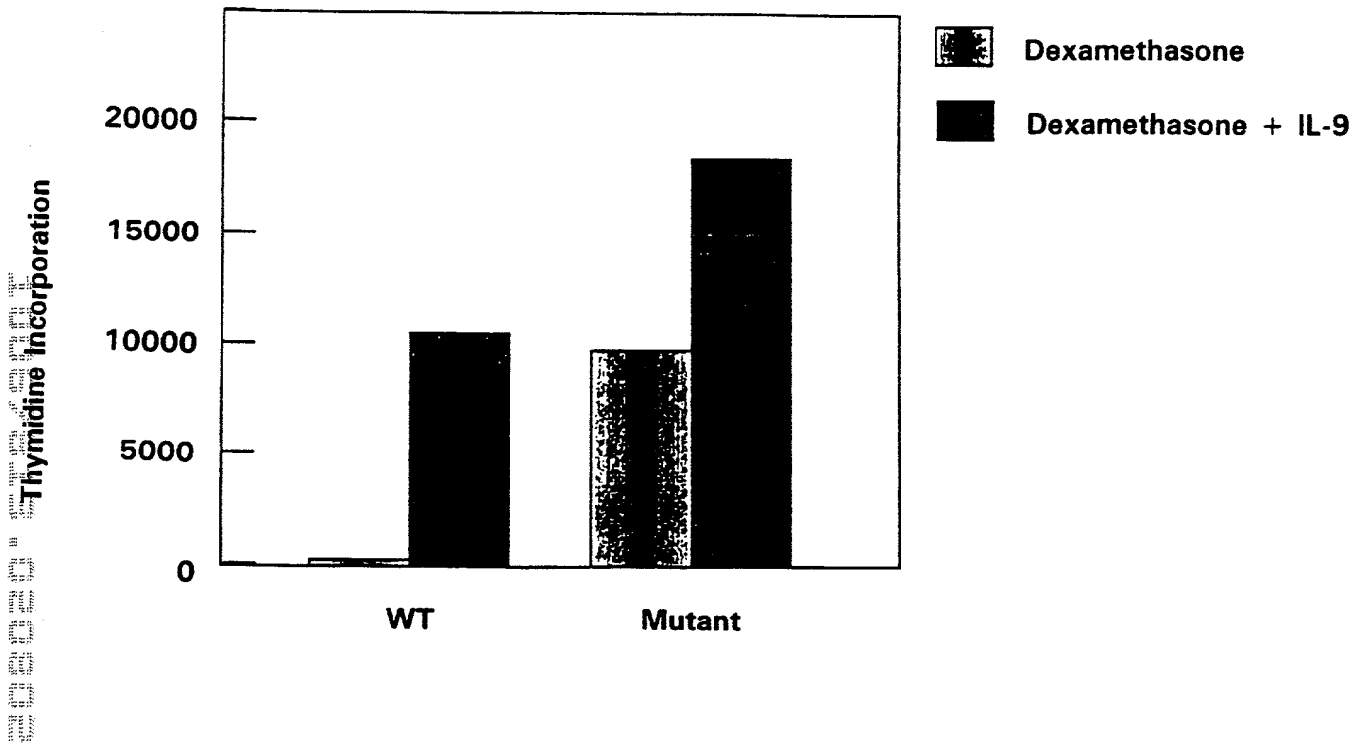

Thymidine incorporation
20000
15000
10000
5000
0
WT
Mutant
Dexamethasone
Dexamethasone + IL-9

Figure 14

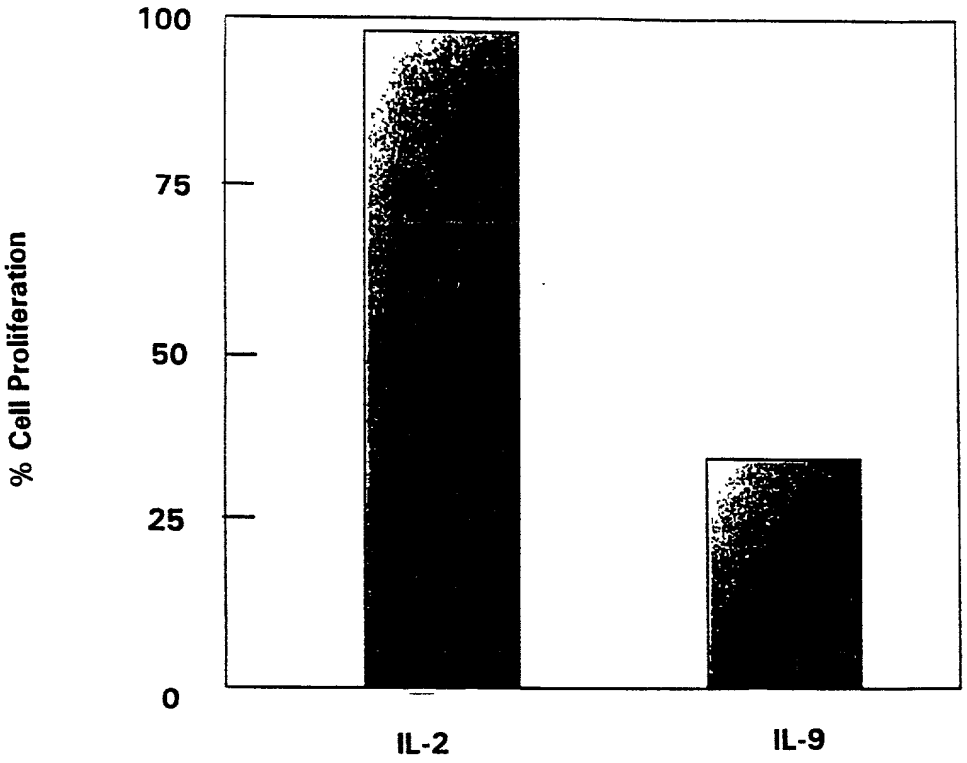



Figure 15

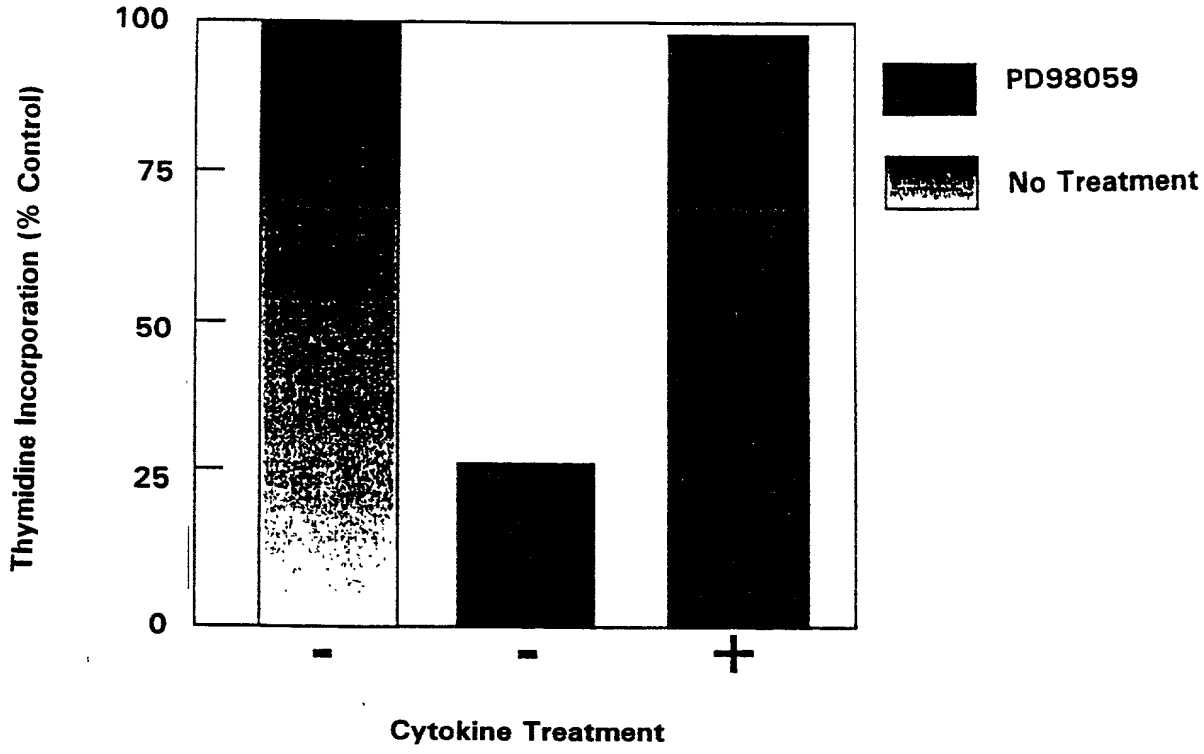

100
75
50
25
0
Thymidine Incorporation (% Control)
-
-
+
Cytokine Treatment
PD98059
No Treatment

Figure 16

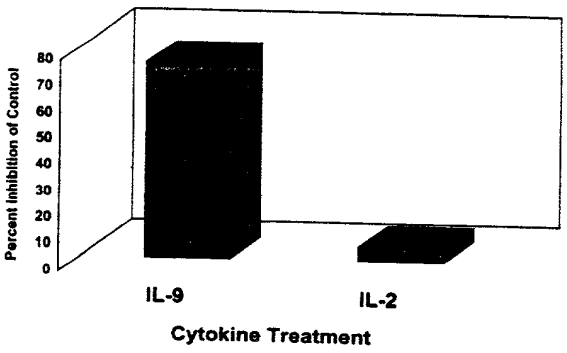

Percent Inhibition of Control
80
70
60
50
40
30
20
10
0
IL-9
IL-2
Cytokine Treatment

**Figure 17**

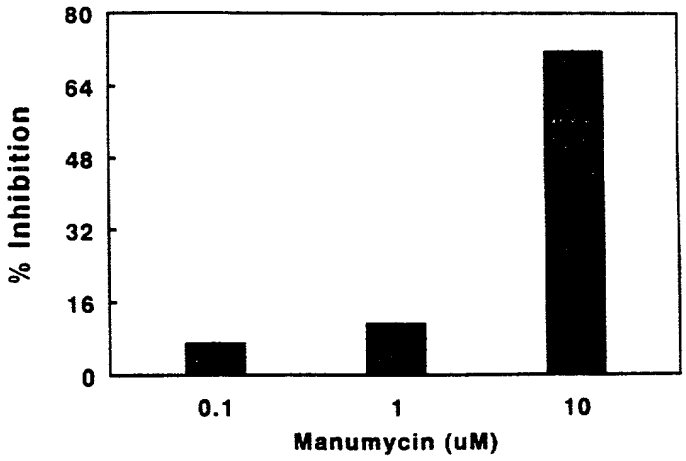



Figure 18

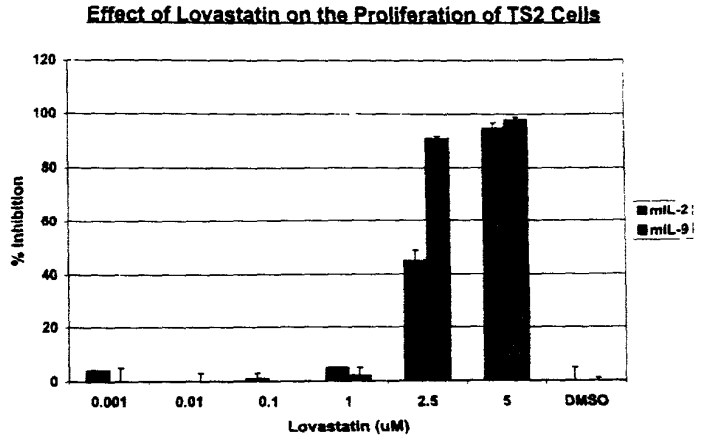
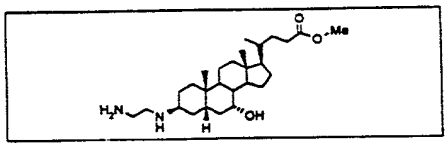
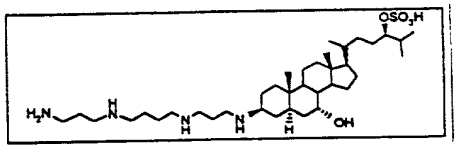

Effect of Lovastatin on the Proliferation of TS2 Cells
120
100
80
60
40
20
0
% Inhibition
0.001
0.01
0.1
1
2.5
5
DMSO
Lovastatin (uM)
mIL-2
mIL-9

Figure 19

1409



1436



1569

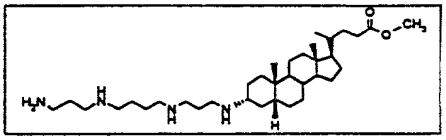


**Figure 20**

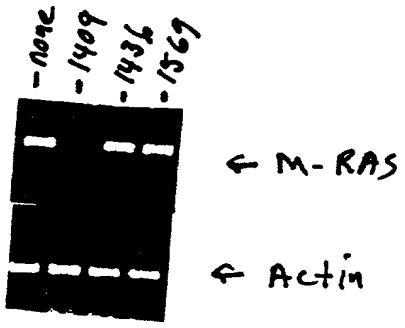



**Figure 21**

# Lovastatin Inhibition of M-RAS Prenylation

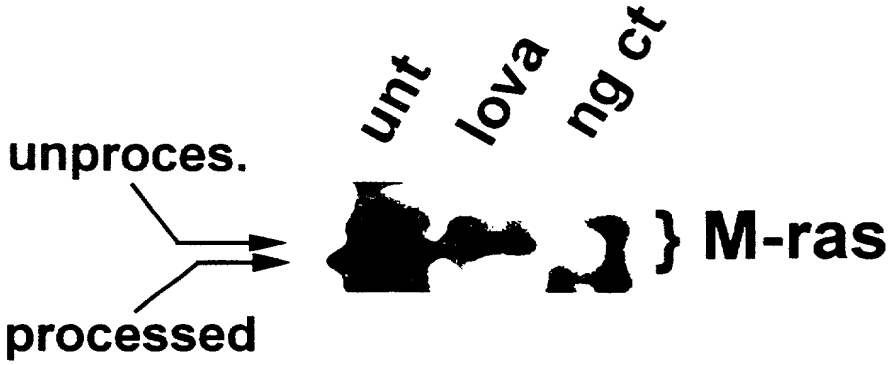



Figure 22